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Ambient Water Quality Criteria Document Addendum for Hexachlorocyclopentadiene

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Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority Pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five jears. These addenda represent an updated literature search current as of 1988, plus additional information form Agency files and Program Offices. This addendum is to update the existing Ambient Water Quality Criteria Document for Hexachlorocyclopentadiene.

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ADDENDUM FOR HEXACHLOROCYCLOPENTADIENE

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PREFACE

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. The first draft of this addendum was prepared by Syracuse Research Corporation under contract no. 68-C8-0004.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CRAVE	Carcinogen Risk Assessment Verification Endeavor
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity
TLV	Threshold limit value
TWA	Time-weighted average

INTRODUCTION

Under Section 304(a)(1) of the Clean Water Act of 1977 as amended in 1987, the U.S. EPA is required to publish criteria for water quality accurately reflecting the latest scientific knowledge regarding the effects on health and welfare that may occur from the presence of pollutants in any body of water, including groundwater. In accordance with the 1977 act, Ambient Water Quality Criteria Documents (AWQCDs) were developed in 1980 for 65 toxic pollutants or classes of pollutants listed under Section 307(a)(1).

These addenda are intended to serve as an update of the original AWQCDs. The addenda provide the Agency with the latest scientific assessments of potential health hazards associated with these pollutants and serve as guidelines for modifying the current (1980) AWQCDs.

The human health criteria in these addenda are based on Agency verified risk assessment values when available. These values consist of reference doses (RfD) for those chemicals believed to be systemic toxicants (i.e., do not induce cancer) and cancer risk factors for those thought likely to cause cancer in humans. The verification process consists of a review and consensus of risk assessment values provided by an Agency workgroup consisting of scientists from each of the major Agency offices. Assessments for noncarcinogens are verified by the RfD workgroup and those for carcinogens are verified by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) workgroup. If such values are not available, the criteria are based on the most recent Agency health assessment. In the absence of any appropriate Agency value, RfD values or cancer risk factors are derived by current Agency methods if adequate new data are available, and criteria are recommended based on the proposed RfD or risk factor.

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is derived by dividing a NOAEL or LOAEL for subchronic or chronic exposure by standard uncertainty factor(s) times an additional uncertainty factor:

$$RfD = \frac{\text{NOAEL or LOAEL}}{UF(s) \times UF}$$

The standard uncertainty factors are applied to reflect the various types of data used to estimate RfDs. An uncertainty factor of 10 is used to account for variations in human sensitivity when extrapolating from valid human studies involving long-term exposure of average, healthy subjects. An additional 10-fold factor is used for each of the following: to extrapolate from long-term animal studies to the case of humans, to extrapolate from subchronic animal studies to chronic exposure, and to extrapolate from a LOAEL to a NOAEL. An additional uncertainty factor of >0-10 may be applied to reflect professional assessment of the uncertainties of the study and data base not explicitly addressed by the standard uncertainty factors (i.e., completeness of the overall data base). The default value for the additional uncertainty factor is 1.

In assessing the carcinogenic potential of a chemical, the U.S. EPA classifies the chemical into one of the following groups according to the degree of evidence in epidemiological studies and animal studies: Group A - Human Carcinogen, Group B - Probable Human Carcinogen [limited evidence in humans with or without sufficient evidence in animals (Group B1) or inadequate evidence in humans with sufficient evidence in animals (Group B2)]; Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); Group D - Not Classifiable as to

Human Carcinogenicity (inadequate or no evidence); Group E - Evidence of Noncarcinogenicity for Humans. Quantitative carcinogenic risk assessments are performed for chemicals in Groups A and B, and on a case-by-case basis for chemicals in Group C. Upper-bound cancer unit risks (slope values) are estimated through the use of mathematical extrapolation models. Most commonly for animal data, the linearized multistage model with a 95% upper confidence limit is used to provide a low-dose estimate of cancer risk. The cancer risk is characterized as an upper-limit estimate (i.e., the true risk to humans, while not identifiable, is not likely to exceed the upper-limit estimate and in fact may be lower). Alternative risk models to the multistage model, such as the one-hit, Weibull, Logit or Probit model, are available and may be used when the evidence indicates that they may be more appropriate. In the absence of such evidence, the Agency recommends the linearized multistage model to provide consistency of approach and an upper-bound on the potential carcinogenic risk. In the case where human data are used for quantitative risk assessment, an upper-bound estimate rather than a 95% upper-bound estimate is used when low-dose linearity is assumed.

In the development of this Addendum to the AWQCD on hexachlorocyclopentadiene, recent Agency assessments have been consulted. A computerized literature search was conducted to cover studies published more recently than the latest Agency assessment (i.e., published in 1987 to 1988). New key studies have been evaluated.

REVIEW OF NEW DATA

Toxicologic/Carcinogenic Effects

Subchronic studies on the oral administration of hexachlorocyclopentadiene in rats and mice were performed by SRI (1981a,b) under contract for NTP and were also reported by Abdo et al. (1984). Hexachlorocyclopentadiene (97.4% pure) in corn oil was administered by gavage to F344 rats (10/sex/group) 5 days/week for 13 weeks at doses of 0, 10, 19, 38, 75 or 150 mg/kg. Mortality, body weights, organ weights and tissue pathology were evaluated. At the 150 mg/kg level, deaths of six male rats were attributed to the test chemical. A dose-related reduction in rate of body weight gain was observed that was statistically significant in males at 38 mg/kg and in females at 75 mg/kg. Increased kidney-to-brain weight ratios were observed in female rats at $\geq$75 mg/kg and increased liver-to-brain weight ratios were observed in females at $\geq$38 mg/kg. Forestomach lesions described as hyperplasia, acanthosis and hyperkeratosis were observed in male rats at $\geq$38 mg/kg and in female rats at $\geq$19 mg/kg. The severity of the lesions increased with dosage. A NOAEL of 10 mg/kg in female rats was derived for this study.

The dose levels of 0, 10, 19, 38, 75, 150 and 300 mg/kg were administered by gavage in corn oil to B6C3F1 mice (10/sex/group) (SRI, 1981b; Abdo et al., 1984). At the highest dose level, all male mice and 3/10 females died. There was a significant decrease in rate of body weight gain in both sexes at dose levels of 150 and 300 mg/kg. There was a significant dose-related increase in liver- and kidney-to-brain weight ratios in female mice at all doses. Females, but not males, had toxic nephrosis at doses $\geq$75 mg/kg. Both sexes had lesions in the forestomach, including ulceration, at dose levels $\geq$38 mg/kg. The NOAEL for mice was 19 mg/kg/day. In 1982, NTP terminated the chronic oral toxicity studies of HEX being conducted by SRI.

At that time it was determined that inhalation was the more relevant route of exposure. No other chronic studies have been reported for HEX.

Other recent oral studies with hexachlorocyclopentadiene include developmental toxicity studies in Charles River CD rats (IRDC, 1978; Root et al., 1983), CD-1 mice (Chernoff and Kavlock, 1982; Gray and Kavlock, 1984; Gray et al., 1986), CF-1 mice and New Zealand white rabbits (Murray et al., 1980). In all of these experiments the test chemical was administered by gavage during organogenesis. Rats treated at 30 mg/kg/day had minimal evidence of maternal toxicity (anogenital staining, but no other clinical signs or effects on body weight gain) but no evidence of fetotoxicity. Neither maternal nor fetal effects were reported in mice at dosages $\leq$75 mg/kg/day. In rabbits, maternal effects (diarrhea, severe weight loss, mortality) were reported at 75 mg/kg/day but not at 25 mg/kg/day. There were no fetal effects at 25 mg/kg/day; however, an increased incidence of offspring with 13 ribs was reported at 75 mg/kg/day.

Several subchronic inhalation studies (Battelle Northwest Laboratories, 1984; Abdo et al., 1986; Abdo, 1987; Clark et al., 1982; Rand et al., 1982a,b) are also available and have been reviewed in U.S. EPA (1984a,b, 1988a). Generally, the lungs, liver and kidney appear to be the target organs of inhalation exposure to hexachlorocyclopentadiene, and the lung appears to be the critical organ. Intermittent (6 hours/day, 5 days/week) exposure to $\geq$0.5 ppm (5.6 mg/m^3) was associated with death in rats (Clark et al., 1982); similar exposure to 0.15 ppm (1.7 mg/m^3) was associated with histopathologic changes in the respiratory epithelium of mice (Abdo et al., 1986). Subtle ultrastructural changes were observed in the Clara cells of rats at 0.01 ppm (0.1 mg/m^3). An NTP inhalation 2-year bioassay study

has recently been completed. Histological examinations of tissues are presently being conducted. Preliminary results are expected in December of 1989.

Several occupational studies have been reported for HEX since the 1980 AWQCD was published (Morse et al., 1978; Wang and McMahon, 1979; Buncher et al., 1980; Shindell et al., 1980, 1981). In general, occupational exposure of plant workers at concentrations <1000 ppm have resulted in eye, throat and skin irritation as well as headaches, nauseau, chest pains and labored breathing. Epidimiological studies of these plant workers have revealed no increase in mortality rate due to HEX exposure; however, a significant increase was reported in the incidence of cerebrovascular disease. This increase, however, could not be attributed solely to HEX exposure.

Because of the lack of carcinogenicity data for oral or inhalation exposure of animals or humans to hexachlorocyclopentadiene, the chemical has been assigned to CAG Group D - not classifiable as to carcinogenicity to humans (U.S. EPA, 1984b, 1988a).

Bioconcentration Factor (BCF)

Pertinent new information concerning the bioconcentration factor for hexachlorocyclopentadiene is currently undergoing Agency review. The BCF value of 4.34 determined in U.S. EPA (1980) will be used until this review is completed.

QUANTIFICATION OF EFFECTS

The 1980 ambient water quality criterion for hexachlorocyclopentadiene was 1 µg/ℓ (U.S. EPA, 1980), based on the undesirable taste and smell of the substance, because adequate toxicity data were not available at that time. However, the desired level for protection of human health could have been as high as 206 µg/ℓ based on the available information.

U.S. EPA (1985) has verified an oral RfD for hexachlorocyclopentadiene of 7 µg/kg/day. This RfD is based on the rat toxicity study described in the previous section (SRI, 1981a,b; Abdo et al., 1984) in which the NOAEL in female rats was 10 mg/kg. From these data, new criteria based on health effects were calculated. Using the previously derived BCF of 4.34, assuming consumption of 2 ℓ of water and 0.0065 kg of fish and shellfish/day and a reference human body weight of 70 kg, a criterion of 242 µg/ℓ can be calculated. For consumption of fish and shellfish only, the criterion is 17.4 mg/ℓ. These criteria, based upon health effects, are substantially higher than the previously derived criterion of 1 µg/ℓ based on organoleptic effects.

The health effects associated with oral exposure to HEX have recently been reviewed by the EPA Science Advisory Board Halogenated Organics Subcommittee (May 17, 1989). It was the conclusion of the SAB that the "RfD of 0.007 mg/kg/day be accepted as the basis of the Drinking Water Standard for HEX as it appears to be based on sound scientific data."

EXISTING STANDARDS AND CRITERIA

The current oral RfD in IRIS (U.S. EPA, 1985) is 7 µg/kg/day for a human, based on the rat subchronic data reported by Abdo et al. (1984).

The RQ under the CERCLA guidelines is 10 pounds, based on aquatic toxicity (U.S. EPA, 1987).

The ACGIH (1987) recommended TLV-TWA of 0.01 ppm or ~0.1 mg/m^3 is intended to protect against all irritation and systemic toxicity (ACGIH, 1986).

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